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Update on the pathophysiology and medical treatment of peripheral artery disease

Jonathan Golledge[1,2,3]

Abstract | Approximately 6% of adults worldwide have atherosclerosis and thrombosis of the lower limb arteries (peripheral artery disease (PAD)) and the prevalence is rising. PAD causes leg pain, impaired health-related quality of life, immobility, tissue loss and a high risk of major adverse events, including myocardial infarction, stroke, revascularization, amputation and death. In this Review, I describe the pathophysiology, presentation, outcome, preclinical research and medical management of PAD. Established treatments for PAD include antithrombotic drugs, such as aspirin and clopidogrel, and medications to treat dyslipidaemia, hypertension and diabetes mellitus. Randomized controlled trials have demonstrated that these treatments reduce the risk of major adverse events. The drug cilostazol, exercise therapy and revascularization are the current treatment options for the limb symptoms of PAD, but each has limitations. Novel therapies to promote collateral and new capillary growth and treat PAD-related myopathy are under investigation. Methods to improve the implementation of evidence-based medical management, novel drug therapies and rehabilitation programmes for PAD-related pain, functional impairment and ischaemic foot disease are important areas for future research.

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Peripheral artery disease (PAD) is characterized by stenosis or occlusion of the arteries supplying blood to the lower limbs. PAD is a growing global public health problem owing to its high and rising prevalence and association with adverse outcomes, including functional decline, immobility and cardiovascular events, such as myocardial infarction, stroke, amputation and death[1–5]. In this Review, I summarize the epidemiology, presentation, outcomes, pathophysiology and current treatment of PAD, and outline the ongoing research into new medical treatments for this condition. My aim is to provide a broad introduction and update for the scientists and clinicians who manage patients with PAD and also for researchers who are interested in advancing our understanding of the disease. This Review is timely for several reasons. There has been slow, but steady, recognition that targeted and unique medical treatments and rehabilitation are needed to effectively manage the enormous and growing burden of PAD[5,6]. Early recognition and effective treatment of PAD can substantially reduce the risk of adverse events[1]. Furthermore, medical treatment options have expanded over the past decade, during which time large populations of patients with PAD have been specifically recruited into several clinical trials testing novel drugs, such as low-dose rivaroxaban[7–9]. Wide dissemination of these new treatment options is, therefore, important. The opportunity also exists to address many of the remaining challenges in the management of PAD[6,10], such as the need for effective medications for symptoms and functional impairment, new rehabilitation programmes and new treatments to reduce the risk of major adverse events and functional decline[6]. Given the broad scope of this Review, all areas could not be covered in depth, and interested readers are referred to reviews that focus on individual areas for more details. TABLE 1 provides definitions for some of the key terms used throughout this Review[3,6,11–15].

Epidemiology

The epidemiology of PAD was examined in detail in a 2019 systematic review of 118 articles reporting findings from 33 countries[5]. FIGURE 1 illustrates the estimated prevalence of PAD in men and women in high-income countries (HICs) and in low-income and middle-income countries (LMICs) reported in that review[5]. The prevalence of PAD increased with age, and this age-related rise was more marked in HICs than in LMICs[5] (FIG. 1). The prevalence of PAD in women was greater than in men for many age ranges (FIG. 1). Overall, an estimated 237 million people aged ≥25 years had PAD worldwide in 2015, of whom 73% were in LMICs[5]. This number includes many young people. For example, an

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Key points

- Peripheral artery disease (PAD) is present in 6% of adults and is associated with leg pain, walking impairment and high risk of major adverse cardiovascular events, including amputation and death.
- PAD usually presents with leg pain, ischaemic ulceration or gangrene and is usually caused by atherosclerosis and thrombosis, although all current animal models use surgically created hindlimb ischaemia.
- Treatment options for the leg symptoms of PAD include cilostazol, exercise therapy and revascularization, with novel therapies under investigation including autologous cell therapy, organic nitrates and antioxidants.
- Antithrombotic and LDL-cholesterol-lowering medications, smoking cessation and treatment of hypertension and diabetes mellitus reduce the risk of major adverse events, but programmes to improve uptake of these measures are needed.

estimated >18 million people aged 45–49 years had PAD in LMICs[5]. The total number of people with PAD was estimated to have risen by 17% from 202 million in 2010 (REFS[5,16]). The relative increase was much more marked in LMICs (23%) than in HICs (4%)[5].

Song and colleagues[5] also performed a meta-analysis of risk factors for PAD examined in multivariable analyses in at least three studies. TABLE 2 shows a comparison of the findings from studies in HICs and LIMCs. In all countries, increasing age, current or former smoking, hypertension, diabetes mellitus, coronary heart disease, stroke, increasing waist circumference and high circulating levels of the inflammatory marker C-reactive protein (CRP) increased the risk of PAD[5]. For most risk factors, the odds ratio (OR) was similar in HICs and LIMCs. Notable exceptions were male sex, current alcohol drinking, increased systolic blood pressure, hypercholesterolaemia and obesity (TABLE 2).

The findings that women have a higher prevalence of PAD than men in many age ranges has raised alarm, because awareness and focus on PAD in women is much lower than for men[17]. Oestrogen was previously proposed to have a favourable effect on the vascular system[18], and the prevalence of smoking, hypertension and diabetes were much higher in men than in women in LMICs[5]. Therefore, the cause of the high prevalence of PAD among women was not immediately apparent. Of note, clinical trials of new drugs and other agents have frequently included a much greater proportion of men than women[19]. For example, in the UK Heart Protection study[19] (conducted in 1994–1997), 74% of participants with PAD were men. Even in the much more recent COMPASS trial[9] (conducted in 2013–2016), <30% of participants with PAD were women. Given that conventional risk factors did not seem to explain the excess risk of PAD in women, less-established risk factors might be involved. In a 2017 Cochrane review, the risks associated with long-term hormone therapy were examined using data from 22 studies involving 43,637 women[20]. Combined oestrogen and progestogen continuous therapy increased the risk of a coronary event by 1–5 per 1,000 people in healthy women, but no data were available on PAD[20]. Sex-related differences might also exist in the relationship between metabolic syndrome and inflammation. A significantly stronger correlation between increased concentrations of CRP in the plasma and increasing BMI has been reported for women than for men[21]. In addition, sex-related differences in normal tibial artery blood pressure have been proposed, so that different diagnostic criteria for PAD might be needed in men and women[22]. Further efforts are needed to raise awareness, identify the underlying causes and establish effective ways to reduce the burden of PAD in women.

Another important focus for research is to investigate the reasons for the varying PAD prevalence in different geographical regions[4,5,23] and ethnic groups[23,24]. The prevalence of PAD in African American women aged 60–69 years has been estimated to be 9%, rising to 35% in those aged ≥80 years[23]. By contrast, the prevalence of

Table 1 | **Definitions of the key terms used in this Review**

Term	Definition	Alternative terms	Refs
Peripheral artery disease	Stenosis or occlusion of the arteries that supply blood to the lower limbs, usually diagnosed using the ABI or with duplex ultrasonography	Lower extremity arterial disease; peripheral vascular disease	6,11–13,15
Intermittent claudication	Pain in the calf during walking and relieved by rest, classically defined using the Rose questionnaire	None	14
Ischaemic rest pain	Rare presentation of peripheral artery disease with constant foot pain made worse by raising the leg and improved by dependency, present for >2 weeks and accompanied by evidence of severe ischaemia (ABI < 0.4, absolute ankle pressure < 50 mmHg, toe pressure < 30 mmHg or transcutaneous partial pressure of oxygen < 30 mmHg)	None	15
Chronic limb-threatening ischaemia	Objective evidence of peripheral artery disease in association with ischaemic rest pain or tissue loss including ulceration or gangrene	Critical limb ischaemia	15
Ischaemia not threatening the limb	Presentations of peripheral artery disease that do not qualify as chronic limb-threatening ischaemia. These presentations include intermittent claudication and also less-recognized symptoms such as leg pain not related to walking that is present at rest but does not qualify as ischaemic rest pain. The latter is common in people with diabetes mellitus and neuropathy and is associated with poorer walking performance and faster functional decline than intermittent claudication	Without chronic limb-threatening ischaemia	3

ABI, ankle–brachial index.

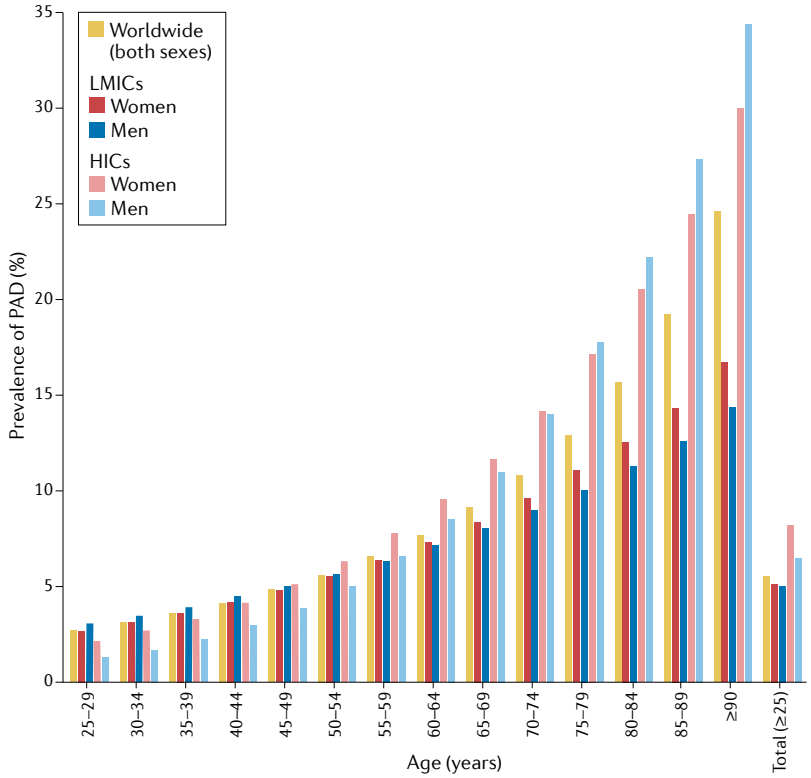

Fig. 1 | **Prevalence of PAD in relation to age and country income.** The prevalence of peripheral artery disease (PAD) increases with age, particularly in high-income countries (HICs) compared with low-income and middle-income countries (LMICs). Prevalence of PAD reported as percentage. The graph was generated using data from REF.[5].

PAD was 5% and 18% in non-Hispanic white American women aged 60–69 years and ≥80 years, respectively[23]. In a systematic review of data from the general population of the USA, the prevalence of PAD was consistently high among African American men and women and Hispanic women, whereas Hispanic men had an intermediate risk and Asian American men had the lowest risk[24]. Our understanding of genetic risk factors for PAD was advanced in 2019 by the Million Veteran Program genome-wide association study[25], in which 19 genetic loci associated with PAD at genome-wide significance were identified. These loci included a variant allele for the gene encoding lipoprotein(a), which had an OR of 1.26 (95% CI 1.22–1.30) for PAD[25]. Some of the identified alleles seemed to amplify the risk of PAD conferred by established risk factors such as diabetes, nicotine dependence and high LDL-cholesterol concentrations because, when the findings were adjusted for these risk factors, some of the alleles had a much weaker association with PAD[25]. The analysis also showed that 11 of the 19 loci identified were associated with coronary and cerebral artery disease as well as PAD[25]. Four of the variants, including the factor V Leiden variant in the *F5* gene, were unique to the risk of PAD[25]. Further analysis in participants of European ancestry suggested that the factor V Leiden variant conferred a particularly high risk of chronic limb-threatening ischaemia (CLTI) (OR for tissue loss 1.57, 95% CI 1.34–1.83) and major amputation (OR 1.62, 95% CI 1.16–2.26)[25]. A strong interaction was found between the factor V Leiden variant and smoking; individuals with the variant who were current smokers were at a particularly high risk of PAD[25]. Other novel and underappreciated risk factors for PAD under investigation include anxiety and depression, lead and cadmium exposure and air pollution[6].

Presentation, diagnosis and outcomes

Presentation

The classical symptom of PAD is intermittent claudication, although studies suggest that most patients with PAD do not have this symptom[11–13,26]. In a community study conducted in the USA, in which 6,979 participants (aged >70 years, or aged 50–69 years with diabetes or a history of smoking) were screened using the ankle–brachial index (ABI), only 11% of patients with PAD had intermittent claudication[27]. In another US study of 415 patients with PAD, 49% had atypical symptoms (such as leg pain unrelated to exercise), 32% had classical intermittent claudication and 19% were asymptomatic[3]. A less common, but more concerning, symptom of PAD is ischaemic rest pain[15] (TABLE 1). Patients with severe ischaemia can also present with tissue loss, such as toe gangrene or foot ulcers[15]. The prevalence of diabetes-related foot ulcers is increasing[28]. In 2016, the global burden from diabetes-related foot ulcers was estimated to be 2.5 million years lived with disability, which represents an increase of >100% since 1990 (REF.[28]). In some hospital series of diabetes-related foot ulcers, PAD has been diagnosed in 50–86% of patients[29–31].

Diagnosis

Under-diagnosis of PAD is a recognized problem, partly because most patients are asymptomatic or have less well-recognized symptoms[27]. The main diagnostic tests for PAD recommended in current guidelines are ABI and duplex ultrasonography, with CT and magnetic resonance angiography used in selected situations (for example, when unusual causes of leg ischaemia are suspected)[11–13,15]. ABI is the classic and cheapest diagnostic test. A hand-held Doppler probe is used to compare the cuff pressure needed to occlude the signal in the brachial arteries (brachial pressure) with that for the tibial arteries at the ankles (ankle pressure)[32,33]. The ankle pressure is divided by the brachial pressure to give the ABI[32,33]. A ratio of ≤0.9 is abnormally low and diagnostic for PAD, 0.91–0.99 is borderline, 1.00–1.40 is normal and ≥1.40 is abnormally high as a result of noncompressible, calcified, tibial arteries[33,34]. Patients with borderline and abnormally high ABI require further investigation, which can include measurement of toe–brachial index, with a ratio of ≤0.7 used (albeit rarely) to confirm the diagnosis of PAD[11]. On imaging, stenoses of ≥50% or occlusions in one or more lower limb arteries is diagnostic for PAD[11–13,15].

Outcomes

Function and quality of life. PAD causes functional limitations, such as reduction in distance walked during a 6-min walking test (6MWT), reduced scores for the short physical performance battery assessment and reduced objectively measured physical activity[35] (TABLE 3). Patients with PAD have significant reductions in the physical

Revascularization
Minimally invasive interventional (such as stenting) or open surgical (such as endarterectomy) procedures to improve distal blood supply.

domains of the commonly used short form-36 health-related quality of life (QOL) tool compared with healthy age-matched and sex-matched individuals (TABLE 3). Shorter 6MWT distance has been correlated with worse health-related QOL and greater likelihood of disease progression[36,37]. Mobility loss (defined as the inability to walk up and down a flight of stairs or a quarter of a mile without assistance) has been reported to develop in approximately one-third of patients with PAD over 1–4 years of follow-up[38,39]. The risk of mobility loss is greater for patients who first present with severe ischaemia and functional impairment[38,40]. Short 6MWT distance has also been associated with increased risk of mobility loss and major adverse cardiovascular events (MACE), including myocardial infarction, stroke and death[37,41–44].

Symptom progression and functional decline. Interpreting studies on the progression of PAD is challenging because of marked differences in definitions and monitoring[45]. In a systematic review, only nine studies published between 1991 and 2009 reported the incidence of progression of PAD-related leg symptoms[45]. These studies and, therefore, the systematic review had many limitations, including mixing patients with PAD and those with other cardiovascular diseases, lack of clear definitions for symptom and disease progression as well as heterogeneity in the PAD presentations included, treatments used, data collection methods and follow-up[45–47].

The EUCLID trial[48] overcame many of these limitations. Patients with PAD ($n = 12,759$) were assessed at enrolment using the Rutherford classification: stage 0 (asymptomatic, 19.2% of the patients), stage 1 or 2 (mild or moderate intermittent claudication, 53.9%), stage 3 (severe intermittent claudication, 22.7%), stage 4 (rest pain, 2.5%), stage 5 (minor tissue loss, 1.3%) and stage 6 (major tissue loss, 0.4%)[48]. Notably, 95% of asymptomatic patients had undergone previous revascularization for symptomatic PAD[49]. After 1 year, 25%, 64% and 11% had improvement, no change or worsening of Rutherford symptom classification, respectively[48]. Age >65 years (OR 1.13, 95% CI 1.06–1.20), diabetes (OR 1.16, 95% CI 1.03–1.32) and lower ABI (OR 1.11, 95% CI 1.08–1.15 per 0.1 decrease) were independently associated with symptom progression[48]. Patients who took statins were less likely to have symptom progression (OR 0.84, 95% CI 0.73–0.97)[48]. The findings from the EUCLID trial suggest that a small proportion of patients had symptom progression, but a few caveats should be noted. First, almost 75% of participants were asymptomatic at recruitment or had mild-to-moderate symptoms, and most had undergone revascularization. Second, follow-up was limited to 1 year. Third, no functional assessments were performed.

PAD has been demonstrated to be an important risk factor for mobility loss. In the Walking and Leg Circulation Study[50], mobility loss (as defined above) was examined in 666 participants over 5 years. Abnormal ABI was associated with an increased risk of mobility loss, and severe ischaemia (ABI < 0.50) was associated with a 4.16-fold (95% CI 1.58–10.92) increased risk of mobility loss[50]. These findings highlight the serious and progressive functional consequences of PAD.

Amputation. The most feared complication of PAD is amputation of the leg at or proximal to the ankle (major amputation). The risk of this outcome is highly dependent on clinical presentation; patients presenting with intermittent claudication are at low risk (1–7%) compared with those presenting with CLTI (13–33%) over 1–5 years[1,51–60] (TABLE 4). In the EUCLID trial[61], the rate of major amputation in patients with mild symptoms was low (0.6% per year for the entire EUCLID cohort, 3.9% per year for patients with CLTI at recruitment and 0.5% per year for patients without CLTI at recruitment).

Other major adverse events. The high prevalence of polyvascular disease in patients with PAD could partly explain their high risk of MACE and death[1,51,52,55–60,62] (TABLE 4). The EUCLID trial investigators reported that 10% of participants with PAD had a history of both

Table 2 | **Risks factors for peripheral artery disease**

Risk factor	Region	Number of studies	Number of patients	OR (95% CI)
Age (per 10-year increase)	HICs	17	32,609	1.65 (1.37–1.97)
	LMICs	9	84,819	1.28 (1.17–1.41)
Male sex	HICs	12	16,897	0.94 (0.67–1.32)
	LMICs	17	102,846	0.65 (0.51–0.83)
Current smoking	HICs	16	53,559	3.43 (2.58–4.58)
	LMICs	12	82,865	2.15 (1.55–2.97)
Former smoking	HICs	11	31,009	1.94 (1.62–2.32)
	LMICs	6	39,213	1.36 (1.01–1.83)
Current alcohol drinking	HICs	1	2,831	0.53 (0.31–0.90)
	LMICs	6	35,026	0.89 (0.72–1.11)
Hypertension	HICs	17	49,018	1.59 (1.46–1.74)
	LMICs	17	78,504	1.76 (1.42–2.19)
SBP (per 10 mmHg increase)	HICs	4	8,513	1.31 (1.20–1.42)
	LMICs	5	20,196	1.07 (0.78–1.48)
Diabetes mellitus	HICs	19	48 873	1.98 (1.77–2.22)
	LMICs	21	118,223	1.82 (1.49–2.23)
Hypercholesterolaemia	HICs	10	32,221	1.43 (1.18–1.74)
	LMICs	6	31,004	1.20 (0.88–1.63)
Coronary heart disease	HICs	9	13,675	2.18 (1.65–2.86)
	LMICs	4	63,564	1.56 (1.31–1.86)
Previous stroke	HICs	4	6,650	2.78 (1.48–5.22)
	LMICs	2	22,140	2.23 (1.59–3.14)
Obesity (BMI ≥30 kg/m²)	HICs	2	4,731	1.07 (0.64–1.79)
	LMICs	7	31,743	1.76 (1.42–2.18)
Waist circumference (per 1-cm increase)	HICs	1	1,502	1.07 (1.03–1.12)
	LMICs	2	22,599	1.01 (1.00–1.03)
Chronic kidney disease	HICs	5	9,661	1.79 (1.03–3.12)
hsCRP > 3.0 mg/l	HICs	3	23,271	2.20 (1.44–3.36)
	LMICs	1	643	2.01 (0.91–4.44)

Data are from REF.[5]. HICs, high-income countries; hsCRP, high-sensitivity C-reactive protein; LMICs, low-income and middle-income countries; OR, odds ratio; SBP, systolic blood pressure.

coronary heart disease and cerebrovascular disease, and these patients had a much higher risk of MACE (HR 1.99, 95% CI 1.69–2.34) than those with PAD alone[62]. In a cohort of Australian patients with intermittent claudication ($n = 582$) or CLTI ($n = 201$), the incidence of myocardial infarction, stroke and cardiovascular death at 2.5 years was 9.3%, 3.4% and 5.8%, respectively[1]. In the patients with CLTI, the rate of these events was 13.4%, 4.4% and 14.1%, compared with 7.8%, 3.1% and 2.7% in those with intermittent claudication[1].

Patients with PAD frequently undergo revascularization (21.8% and 48.9% at 2.5 years for patients with intermittent claudication or CLTI, respectively, in the study from Australia[1]). In a systematic review of 526,008 patients undergoing revascularization in the USA, an average of 16.4% (95% CI 15.1–17.9%) of patients with PAD were readmitted to hospital within 30 days[63]. Risk factors for readmission included female sex (OR 1.13, 95% CI 1.05–1.21), Black ethnicity (OR 1.36, 95% CI 1.28–1.46), dependent functional status (OR 1.72, 95% CI 1.43–2.06), CLTI (OR 2.12, 95% CI 1.72–2.62), emergency hospital admission (OR 1.75, 95% CI 1.43–2.15), hypertension (OR 1.39, 95% CI 1.26–1.54), heart failure (OR 1.82, 95% CI 1.50–2.20), chronic pulmonary disease (OR 1.19, 95% CI 1.08–1.32), diabetes (OR 1.47, 95% CI 1.32–1.63) and dialysis-dependent renal failure (OR 2.08, 95% CI 1.75–2.48). These complications add to the cost of revascularization, which has been estimated at approximately AUS $16,000 per patient, emphasizing the substantial PAD-related burden on the health system[64].

Table 3 | **Function and health-related quality of life in patients with PAD and intermittent claudication**

Assessment	Patients with PAD ($n = 78$)	Healthy controls ($n = 25$)	*P* value
Demographics and diagnostic tests			
Age	70 (65–75)	70 (66–74)	0.917
Male sex	60 (76.9%)	17 (68.0%)	0.371
BMI	27.8 (24.3–31.3)	25.6 (23.8–29.5)	0.340
Right ABI	0.69 (0.52–0.87)	1.14 (1.08–1.19)	<0.001
Left ABI	0.78 (0.57–0.89)	1.15 (1.06–1.20)	<0.001
Objectively measured function and activity			
6-min walking test distance (m)	373 (311–438)	463 (414–525)	<0.001
Total score for the short physical performance battery	9 (8–11)	12 (10–12)	<0.001
7-day step count	31,905 (21,505–49,598)	55,698 (42,129–75,161)	<0.001
Total time stepping over 7 days (h)	7.0 (5.0–10.8)	11.4 (9.4–14.8)	<0.001
Short form-36 domains			
Physical functioning	38.8 (29.1–46.4)	50.7 (46.4–52.8)	<0.001
Role physical	47.6 (39.5–53.9)	53.9 (50.3–55.7)	<0.001
Bodily pain	39.6 (34.6–44.0)	52.8 (46.0–59.3)	<0.001
General health	39.8 (34.4–47.6)	50.0 (46.4–56.2)	<0.001
Vitality	45.8 (39.5–49.0)	55.3 (49.0–58.5)	<0.001
Social functioning	56.7 (39.9–56.7)	56.7 (56.7–56.7)	0.019
Role emotional	55.2 (41.6–55.2)	55.3 (51.4–55.3)	0.071
Mental health	55.3 (43.5–58.3)	58.3 (49.4–61.2)	0.075
Physical component summary	38.5 (29.2–44.9)	51.3 (47.7–54.6)	<0.001
Mental component summary	55.8 (46.6–60.6)	58.0 (53.3–61.2)	0.213

Compared with healthy control individuals matched to patients by age and sex. Data reported as median (interquartile range) and compared by Mann–Whitney *U* test, or number (percentage) and compared by chi-squared test. Unpublished data from one site involved in a current clinical trial[36]. The short form-36 is a commonly used questionnaire for assessing general (including physical and mental) aspects of health-related quality of life. ABI, ankle–brachial index; PAD, peripheral artery disease.

Predicting risk of major adverse events. CLTI, poor health-related QOL or multiple and severe comorbidities are risk factors for MACE and limb events[2,7,57,62,65–72] (TABLE 5). Worsening Rutherford symptom classification over 1 year, poor risk-factor control and high circulating concentrations of CRP, fibrinogen and D-dimer have been associated with an increased risk of major adverse events[7,48,73–76] (TABLE 5). A systematic review published in 2021 summarized factors associated with amputation-free survival in 17 studies with sample sizes ranging from 65 to 25,635 patients[77]. Commonly reported risk factors for reduced amputation-free survival included presentation with tissue loss, older age and comorbidities, including coronary heart disease, end-stage renal failure and heart failure[77–79].

Models that predict the risk of adverse events have the potential to inform the management of patients with PAD and guide the use of medical therapies[78]. The GermanVasc score was developed to predict death or major amputation using data from a cohort of 87,293 patients with symptomatic PAD (53.5% with intermittent claudication and 46.5% with CLTI)[78]. Separate models were developed for patients with intermittent claudication and CLTI. The factors included in the model for patients with intermittent claudication were age, alcohol abuse, cancer, chronic airway disease, diabetes, dialysis dependence, dyslipidaemia, fluid disorders, male sex and previous hospital admission. The factors included in the model for patients with CLTI were age, arrhythmia, cancer, dementia, dialysis dependence, fluid disorders, gangrene, heart failure and renal impairment. Both models had good predictive accuracy (*c* statistic of ~0.70) for death or major amputation. The score needs to be assessed in other populations to assess its accuracy and clinical value[78].

Pathogenesis

Pathology

PAD is primarily caused by atherosclerosis or thrombotic occlusion of arteries that supply blood to the lower limbs and associated microvascular dysfunction promoted by the risk factors discussed in the 'Epidemiology' section[79] (FIG. 2). Rare causes of leg ischaemia include popliteal entrapment syndrome, cystic adventitial disease, arteritis and artery endofibrosis, which have previously been reviewed[80,81] and are not discussed here. Atherosclerosis is a chronic intimal artery disease[82]. Pathological studies of human and animal arteries suggest that atherosclerosis has several progressive stages involving accumulation of lipids, inflammatory cells and smooth muscle

Table 4 | **Reported adverse event rates in patients with peripheral artery disease**

Study (year)	Inclusion criteria	Number of patients	Follow-up (years)[a]	Major amputation (%)	MACE (%)	Mortality (%)	Ref.
Patients with intermittent claudication							
Narcisse et al. (2021)	All patients at a US university health system in 2015–2016	730	1.0	1.7[b]	NR	11.7	51
Makowski et al. (2021)	All in-patients treated in seven regional health funds in Germany in 2014–2015	42,197	2.0	0.9	NR	8.3	52
Nastasi et al. (2021)	Consenting outpatients in three Australian centres in 2002–2019	582	2.5	1.0	11.7	5.5	1
Djerf et al. (2020)	All patients undergoing revascularization in Sweden in 2008–2012	5,860	3.9	0.7	NR	NR	53
Madabhushi et al. (2021)	Patients not having revascularization at one US centre in 2003–2019	723	5.3	2.0	NR	NR	54
	Patients having revascularization at one US centre in 2003–2019	328	5.3	7.0	NR	NR	
Kim et al. (2021)	Patients having revascularization at one US centre in 2013–2016	448	3.7	1.2	NR	17.9	55
Patients with CLTI							
Verwer et al. (2021)	Patients not eligible for revascularization at one centre in the Netherlands in 2006–2012	150	5.0	33.0	NR	35.0	56
Narcisse et al. (2021)	All patients at a US University health system in 2015–2016	479	1.0	28.5[b]	NR	22.6	51
de Donato et al. (2021)	Consenting patients undergoing revascularization at multiple sites in Italy in 2016–2018	287	1.0	13.2	NR	11.2	57
Wijeyaratne et al. (2020)	Patients having revascularization at one centre in Sri Lanka in 2015–2017	367	1.0	18.2	NR	12.0	58
Nastasi et al. (2021)	Consenting outpatients at three Australian centres in 2002–2019	201	2.5	13.7	22.6	19.6	1
Kodama et al. (2020)	Multicentre recruitment as part of a clinical trial on endovascular and open revascularization in 1999–2004	377	4.1	15.6	NR	37.1	59
Tay et al. (2020)	Patients undergoing endovascular revascularization at one centre in Singapore in 2015–2017	207	1.8	30.0	NR	31.0	60

Studies were selected based on publication in 2020–2021, to reflect contemporary outcomes, and excluding series reporting the results of one interventional device so that the results can be generalized. [a]Reported as median or mean. [b]Not reported whether all amputations or major amputations. CLTI, chronic limb-threatening ischaemia; MACE, major adverse cardiovascular events; NR, not reported.

cells, necrosis, fibrosis, calcification and thrombosis[82,83]. In advanced stages, a fibrous cap covers a large necrotic core that contains prothrombotic cell debris[82,83]. Fibrous cap thinning, plaque erosion and rupture and associated thrombosis occur at advanced stages[83]. Influx of inflammatory cells within the fibrous cap is strongly implicated in promoting plaque erosion and rupture[84], leading to myocardial infarction and ischaemic stroke[84,85]. The evidence to support this model of thrombosis induced by plaque erosion and rupture is based on findings from animal models and human coronary artery samples and, therefore, its relevance to PAD is unclear.

Few histological studies have been performed on samples of peripheral arteries from patients with symptomatic PAD[79,82,83,86]. These studies suggest the presence of marked tibial artery thrombosis without severe atherosclerosis, which is typically found in patients with coronary artery occlusive disease[79,86]. In a study of 75 patients undergoing above or below knee amputation, Narula and colleagues[86] reported that 49% of the arteries with luminal thrombus had no histological evidence of atherosclerosis. These findings suggest the importance of thromboembolism as a mechanism in the development of CLTI. Of note, the artery segments examined in these studies were limited to amputated sites, meaning that selection bias relating to patients and artery segments limit the extent to which the findings can be generalized. Further studies are needed to clarify the pathology of PAD.

Pathophysiology

Atherothrombotic narrowing and occlusion of the lower limb arteries promote changes in the leg circulatory system and tissues[87,88] (summarized in FIGS 2–4). These changes include compensatory responses to maintain tissue perfusion and detrimental effects such as myopathy and tissue necrosis. The effects of ischaemia are outlined below and discussed in detail in other reviews[89–91].

Myopathy
Muscle damage with various causes, including impaired muscle blood supply owing to peripheral artery disease.

Arteriogenesis
The expansion of existing collateral arteries to improve distal blood supply.

Angiogenesis
The sprouting of new capillaries and formation of new networks of small vessels to improve distal blood supply.

Arterial response. In response to leg ischaemia, collateral branches (such as the inferior epigastric artery or the geniculate arteries) can expand to provide alternative blood flow around the affected artery segment[10,87,88]. This early compensatory mechanism, known as arteriogenesis, explains the spontaneous improvement in limb blood supply within 1–2 weeks of femoral artery occlusion[10,87,88]. Large collateral arteries are commonly seen on the angiograms of patients with PAD[92]. Enlargement of the collateral arteries is believed to be stimulated by increases in shear stress and collateral flow resulting from the distal occlusion, which promotes release of nitric oxide (NO) and further increases collateral flow[10,87,88,93] (FIG. 3). Studies in animal models suggest that upregulation of endothelial adhesion molecules in response to increased collateral flow promotes monocyte recruitment and release of extracellular matrix remodelling enzymes such as matrix metalloproteinases, chemokines and growth factors[10,87,88,93] (FIG. 3). These changes have been proposed to promote growth of pre-existing arterioles[94]. A slower compensatory response to ischaemia that develops over ≥1 month involves the formation of new capillary networks through angiogenesis[10,94–96]. This process is thought to be stimulated by the upregulation of growth factors in response to tissue hypoxia (via hypoxia-related factors), promoting the recruitment of bone-marrow-derived cells (including monocytes and progenitor cells) to the occluded area. This cascade stimulates the expression of genes encoding angiogenesis-promoting proteins, such as vascular endothelial growth factor (VEGF)[10], and leads to the development of a new network of capillaries and small vessels (FIG. 4). However, these compensatory changes are often inadequate or not evident[10,94,96].

Lower extremity muscle pathology. CT and histology studies suggest that PAD-related leg ischaemia leads to pathological changes in leg muscles[89]. Observational studies have demonstrated that ABI < 0.50 or presentation with CLTI is associated with reduced calf muscle area, volume and density, and increased fat percentage[97,98]. An electron microscopy study showed that 14 patients with intermittent claudication had lower capillary density and mitochondrial volume and thicker basement membranes within the vastus lateralis muscle than did 10 age-matched control individuals[99]. These findings were confirmed in an immunofluorescence study, in which capillary density within biopsy samples of the gastrocnemius muscle was lower among 37 patients with PAD than in 29 younger healthy control participants[100]. By contrast, another study reported significantly greater capillary density in gastrocnemius muscle biopsy samples from 12 patients with CLTI than in samples from 12 people with no leg ischaemia[101]. The discrepancy between these findings could be related to the small sample sizes or to various methodological factors.

Table 5 | **Reported risk factors for major adverse events in patients with PAD**

Risk factor	Events				Refs
	Mortality	MACE	MALE	Major amputation	
Male sex	1.13 (1.10–1.16)	1.10 (1.06–1.14)	NR	NR	202
SBP > 125 mmHg (per 10 mmHg)	NR	1.10 (1.06–1.14)	1.07 (1.00–1.15)	NR	70
Diabetes mellitus	2.04 (1.16–3.57)	1.51 (1.11–2.04)		NR	71
Current smoking	NR	2.04 (1.31–3.16)		2.2 (1.8–2.9)	57
Coronary heart disease	NR	1.65 (1.43–1.91)	NR	0.74 (0.47–1.16)	62
Cerebrovascular disease	NR	1.34 (1.15–1.57)	NR	0.83 (0.54–1.27)	62
Estimated GFR < 60 ml/min/m^2	NR	1.45 (1.30–1.63)	NR	0.92 (0.66–1.2)	66
Heart failure	1.39 (1.19–1.63)	1.31 (1.13–1.51)	NR	NR	67
Chronic obstructive pulmonary disease	1.50 (1.27–1.76)	1.30 (1.11–1.52)	0.98 (0.71–1.37)	1.02 (0.63–1.65)	68
Obesity (definition varies)	NR	1.09 (1.03–1.16)	NR	NR	69
Previous revascularization	NR	NR	2.44 (1.71–3.50)	NR	2
Previous amputation	NR	NR	3.77 (2.40–5.93)	NR	2
Statins	0.61 (0.54–0.68)	NR	0.70 (0.61–0.82)	0.65 (0.52–0.82)	76
Improved health-related QOL[a]	NR	0.92 (0.88–0.96)	0.91 (0.83–1.00)	0.86 (0.75–0.98)	72
C-reactive protein	3.49 (2.35–5.19)	1.38 (1.16–1.63)	NR	NR	73,75
Fibrinogen	2.08 (1.46–2.97)	NR	NR	NR	75
D-dimer	2.22 (1.24–3.98)	NR	NR	NR	75
Worsening in Rutherford classification over 1 year	1.29 (1.03–1.62)	1.30 (1.05–1.62)	NR	4.12 (2.46–6.16)	48

Reported relative risk ratios or hazard ratios (95% confidence intervals) selected from published systematic reviews, meta-analyses, large studies or pooled estimates. Preference was given to studies published within the past 3 years. Where available, risk has been adjusted for other factors. Where cells are combined, composite outcomes were reported. [a]Assessed by the Peripheral Artery Questionnaire. GFR, glomerular filtration rate; MACE, major adverse cardiovascular events (including myocardial infarction, stroke and cardiovascular death); MALE, major adverse limb events (including major amputation and peripheral revascularization); NR, not reported; PAD, peripheral artery disease; QOL, quality of life; SBP, systolic blood pressure.

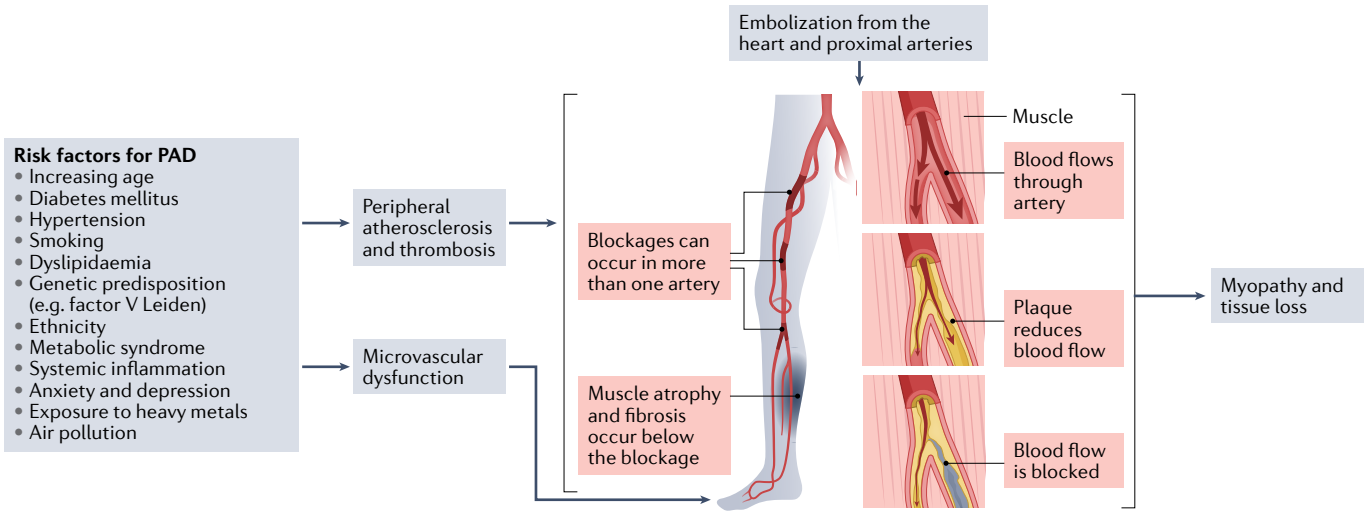

Fig. 2 | **Risk factors, pathological mechanisms and effects of PAD.** The risk factors for peripheral artery disease (PAD) listed on the left of the figure promote development of atherosclerosis, thrombosis, embolization and microvascular dysfunction. Consequent leg and foot ischaemia promotes the development of myopathy. In the presence of severe ischaemia, gangrene or ischaemic ulcers can develop.

Other lower extremity muscle pathology reported in patients with PAD include reduced mitochondrial activity and increased mitochondrial DNA mutations[89]. A mechanism of ischaemia-impaired mitochondria clearance has been proposed on the basis of the abnormal distribution of mitochondria and markers of autophagy observed in muscle biopsy samples from patients with PAD[102]. Some of the lower extremity muscle characteristics associated with PAD — including the increased size of gastrocnemius myofibres and more rapid phosphocreatine recovery time (a marker of mitochondrial function) — have been significantly correlated with better walking performance in patients with PAD[89]. Reduced leg muscle density has been associated with a significantly increased risk of MACE and limb events[42]. This research has implications for the targeting of rehabilitation programmes and novel drug therapies, which are discussed later in this Review.

Microvascular dysfunction. The exact pathological processes that cause gangrene and ulceration in patients with PAD are poorly defined[91]. Evidence is increasing for the involvement of the microvasculature and this aspect is an important focus of study. The cutaneous microcirculation is responsible for skin perfusion, and a healthy microvasculature is thought to be important in skin integrity and function[103,104]. Endothelial function, measured by brachial artery flow-mediated relaxation, has been reported to be significantly impaired in patients with CLTI compared with individuals without PAD[105]. Markers of microvascular dysfunction have also been independently associated with an increased risk of major amputation[104,106]. In 125,000 patients from the Veterans Aging Cohort Study, microvascular disease (defined as previous diagnosis of peripheral neuropathy, proteinuria and retinopathy) was associated with a substantially increased risk of amputation, particularly among patients with PAD (HR 22.71, 95% CI 18.34–28.12)[106]. The association was reported to be independent of diabetes status. A long-term follow-up investigation of 9,371 participants of the Atherosclerosis Risk in Communities (ARIC) study demonstrated that retinopathy at baseline was independently associated with increased risk of developing CLTI (HR up to 5.92, 95% CI 3.00–11.70, depending on the retinopathy measure used)[107].

Therapeutic targets

Important therapeutic targets for PAD include promoting arteriogenesis or angiogenesis, correcting ischaemic leg muscle pathology and limiting the progression of atherothrombosis in the arteries supplying blood to the legs. All animal models of PAD currently involve surgically induced, rather than spontaneous, limb ischaemia; therefore, studies have focused on testing potential methods of promoting angiogenesis or arteriogenesis and, to a lesser extent, modifying ischaemia-induced myopathy.

Animal models

Animal models of PAD involve surgical ligation, excision or occlusion of an artery supplying blood to the limb in pigs, rabbits and rodents[87]. Most animal studies have used acute occlusion or interruption of the femoral artery, but this approach has limitations for studying the effects of drugs, because blood supply to the limb recovers spontaneously over 1–2 weeks[87,108]. A report published in 2020 described a two-stage induction of hindlimb ischaemia (HLI) in dyslipidaemic, apolipoprotein E-deficient mice[108] (FIGS 5,6). During the first stage, two ameroid constrictors were placed around the femoral artery to gradually induce occlusion (FIG. 5). In the second stage, the femoral artery and associated collateral arteries were excised (FIG. 5). HLI was sustained for longer with the two-stage procedure than with the traditional, one-stage model[108] (FIG. 6). Sustained ischaemia was associated with functional impairment in treadmill-measured exercise capacity and reduced activity during an open field assessment, which was not

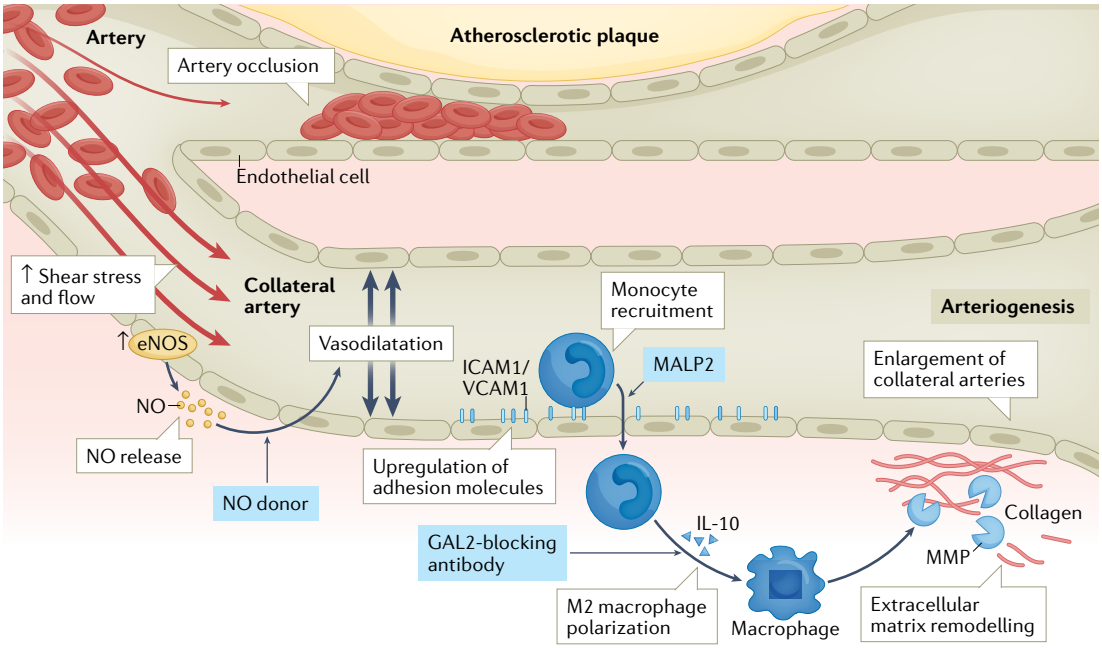

Fig. 3 | **Arteriogenesis induced by lower limb artery occlusion.** Artery occlusion leads to increased flow through narrow collateral artery branches. This increased flow stimulates the upregulation of endothelial nitric oxide synthase (eNOS) in endothelial cells and the release of nitric oxide (NO), which promotes the dilatation of the collateral arteries. Increased flow also promotes the increased expression of endothelial adhesion molecules, such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1), which facilitate the recruitment of monocytes through the collateral artery wall. Inhibition of galectin 2 (GAL2) and the secretion of cytokines such as IL-10 promote the differentiation of monocytes into an M2 macrophage phenotype[114,115]. These macrophages release various matrix remodelling enzymes, such as matrix metalloproteinase 9 (MMP9), which help to increase the diameter of the collateral arteries[114,115]. This process of arteriogenesis can be amplified experimentally (blue boxes) through administering a NO oxide donor, promoting monocyte recruitment (for example, by administering macrophage-activating lipopeptide 2 (MALP2)) and stimulating an M2 macrophage phenotype (for example, with antibodies to GAL2)[111,114,115]. The potential therapeutic approaches illustrated are based on research published in 2020 or 2021 only.

demonstrated in the traditional model[108] (FIG. 6). This finding simulates the functional impairment of patients with PAD (TABLE 3). In the second phase of the study, 6-month-old mice ($n = 30$) that had undergone the two-stage HLI procedure were given daily exercise on a running wheel for 30–45 min for 4 weeks, which led to improved functional capacity (treadmill test) without influencing limb blood supply compared with control mice[108,109]. This benefit of exercise training has also been described in patients with PAD. Exercise training increased the expression of the shear stress responsive element TRPV4 and of VEGF[108]. All these findings support the potential value of using the two-stage HLI model to test novel therapies for functional impairment caused by PAD. The model seems particularly suited to study PAD-related functional impairment, owing to the reduction in ambulatory capacity compared with non-ischaemic control animals[108]. Important functional outcomes include distance and time in ambulation during a treadmill test and distance and speed during an open field test[108]. However, the model was not reported to simulate the tissue loss typical of CLTI. The mice included in the study[108] were C57BL/6, a strain that has been reported to be resistant to the development of gangrene after femoral artery ligation[110]. By contrast, BALB/c mice develop paw gangrene after this procedure[110]. Therefore, BALB/c mice would be better suited than C57BL/6 mice for studies that model CLTI. Ideally, models of spontaneous peripheral atherosclerosis and limb ischaemia need to be developed to provide the most physiologically relevant simulation of human PAD.

Targets for limb ischaemia therapy

TABLE 6 and FIGS 3,4 show examples of therapeutic approaches that have successfully improved limb blood supply, or favourably modified myopathy, in animal models of HLI[111–118]. All studies were published in 2020 or 2021 and used models of acute limb ischaemia that are not representative of the human presentation of chronic ischaemia[111–118]. Successful approaches included upregulating NO, administering progenitor or stem cells and modifying the inflammatory response to ischaemia to promote angiogenesis and arteriogenesis[111,112,114–116,119] (TABLE 6).

Promoting the recruitment of monocytes to the site of arterial occlusion by administering macrophage-activating lipopeptide 2 (MALP2) and promoting monocyte differentiation to M2 macrophages have been reported to promote arteriogenesis in mouse models of HLI[114,115,119] (FIG. 3). Administering endothelial progenitor cells, which express high levels of NADPH oxidase 4, or a NO donor has been reported to upregulate several growth factors, such as proheparin-binding EGF-like growth factor (HBEGF) and stromal cell-derived

factor 1 (SDF1), which promote angiogenesis in mouse and rat models of HLI[111,116] (FIG. 4). Two studies have shown the efficacy of therapies for ischaemia-induced myopathy, including a vector expressing a crucial glycolytic enzyme and mitochondrial transplantation[117,118] (TABLE 6). Readers are referred to other reviews for discussion of treatment targets for reducing MACE, such as novel agents to treat dyslipidaemia, reduce the risk of thrombosis, calcification and inflammation and regress atherosclerotic plaques[120–123].

Translational challenges

Animal models of PAD and the clinical presentation in humans differ in many ways, as previously reviewed[87]. Important limitations of animal studies include the acute, rather than chronic, nature of ischaemia, the absence of sustained ischaemia or clinically important risk factors (such as older age and diabetes), the lack of functional end points and the short duration of treatment[87,108,111,112,114–116]. These limitations might explain the difficulties in translating the positive findings from animal studies into large clinical trials[87]. The use of animal models that are more representative of the clinical presentation of PAD, including functional outcomes, and methods to limit investigator bias through a clinical trial-like design will improve translation[87,108]. A pig model of PAD reported in 2021 involves sustained limb ischaemia, angiogenesis and myopathy[124]. However, the expense of such a model (potentially 20 times the cost of a basic mouse model) could preclude its widespread use. The two-stage HLI mouse model might be a viable alternative, although the validity of this model to identify novel therapies that are also effective in humans needs to be confirmed.

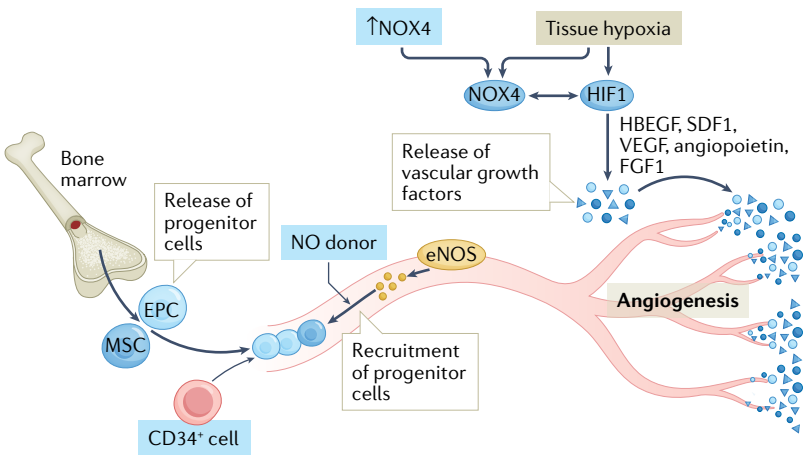

Fig. 4 | **Angiogenesis induced by lower limb artery occlusion.** Tissue hypoxia caused by ischaemia resulting from artery occlusion leads to the upregulation of a variety of hypoxia-related factors, including hypoxia-inducible factor 1 (HIF1), which promotes the release of growth factors such as proheparin-binding EGF-like growth factor (HBEGF), stromal cell-derived growth factor 1 (SDF1), angiopoietin, fibroblast growth factor 1 (FGF1) and vascular endothelial growth factor (VEGF). These factors promote the recruitment of endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs) from the bone marrow. The progenitor cells and growth factors stimulate the sprouting and development of a new network of capillaries and small vessels, promoting improved blood supply to the ischaemic tissue. This angiogenic process can be promoted experimentally (blue boxes), for example, by administration of nitric oxide (NO) donors, the upregulation of NADPH oxidase 4 (NOX4) or the administration of $CD34^+$ progenitor or stem cells[111,112,116]. The potential therapeutic approaches illustrated are based on research published in 2020 or 2021 only.

Established treatments for PAD

Limb symptoms

Three therapeutic options for patients with leg symptoms of PAD are currently in clinical use: the phosphodiesterase type 3 (PDE3) inhibitor cilostazol, various forms of exercise therapy and revascularization.

Cilostazol. Cilostazol increases cAMP levels and has been reported to upregulate NO production and modify the expression of several growth factors and chemokines that stimulate angiogenesis and arteriogenesis[125,126]. A meta-analysis of eight placebo-controlled, randomized trials ($n = 2{,}360$) reported that 100 mg of cilostazol taken twice daily significantly increased treadmill maximum walking distance by a weighted mean of 42 m (95% CI 18–66 m) in patients with intermittent claudication[127]. A meta-analysis of data from four randomized trials and six retrospective cohort studies showed that cilostazol reduced the risk of major amputation (HR 0.42, 95% CI 0.27–0.66) and repeat revascularization (relative risk (RR) 0.44, 95% CI 0.37–0.52) in patients with PAD who underwent revascularization[128]. By contrast, a network meta-analysis published in 2021 showed that cilostazol did not improve walking distance in patients with intermittent claudication[129].

Cilostazol is contraindicated in patients with heart failure, because PDE3 inhibitors have been associated with reduced survival in patients with this condition[126]. The reported adverse effects of cilostazol include palpitations, dizziness and bleeding; a reported 40–53% of users discontinue its use within 3 months[130]. Global uptake of cilostazol is variable, perhaps owing to inconsistent reports of efficacy, intolerance, adverse effects and lack of availability in some countries[131,132].

Exercise therapy. Exercise training, including supervised and structured home-based exercise, is an established treatment to improve function and QOL in patients with symptomatic PAD. These programmes are strongly recommended as first-line treatment in all clinical guidelines[11–13]. Exercise therapy is recommended for all patients without CLTI before revascularization is considered[11–13]. The evidence for exercise therapy, proposed mechanism of action, optimal programme design and implementation have been reviewed in detail[106,133–136]. A meta-analysis of 32 randomized trials involving 1,835 patients with PAD showed that exercise therapy led to a significant improvement in maximum walking distance (mean 82 m; 95% CI 72–92 m)[109]. Most programmes included in these trials involved two or three sessions per week of treadmill walking supervised by a trained health professional[109]. In addition, evidence shows that supervised resistance training improves walking capacity in patients with PAD[137]. A meta-analysis of 18 trials testing various upper and lower body resistance training programmes demonstrated significant improvement in treadmill walking distance[137]. Another meta-analysis of five trials showed that treadmill exercise programmes improved walking

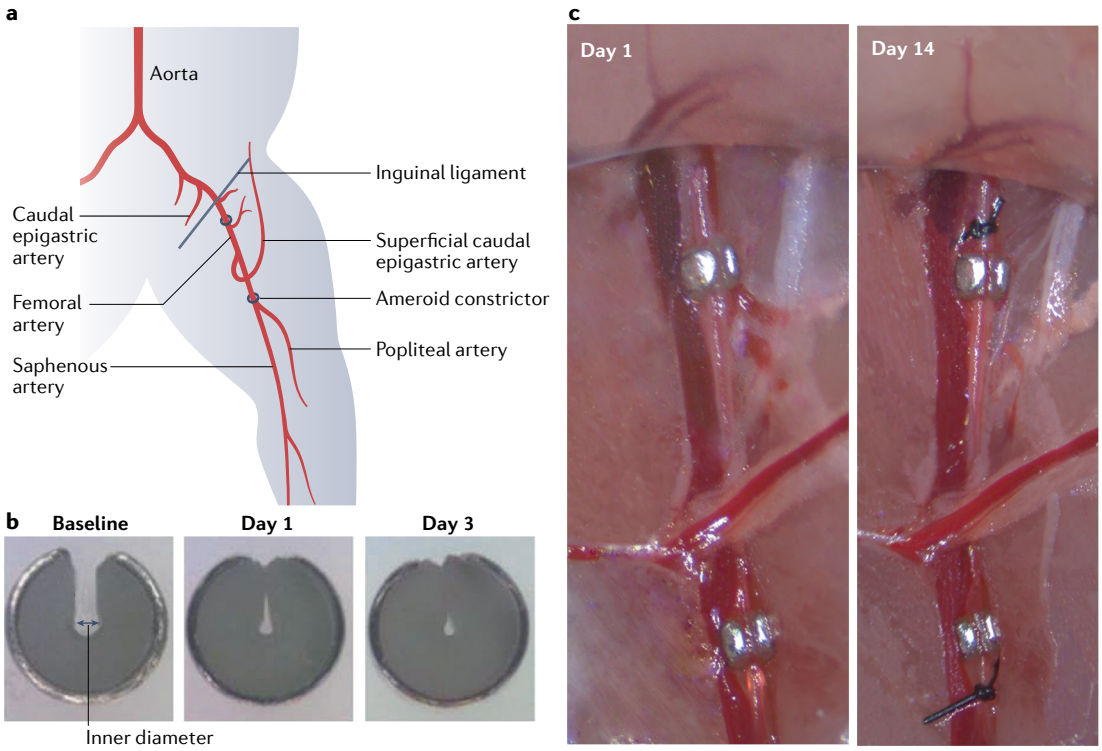

Fig. 5 | **The two-stage hindlimb ischaemia mouse model of peripheral artery disease. a** | Outline of the arteries of a mouse and placement of ameroid constrictors. **b** | How an ameroid constricts an artery over 3 days. **c** | Ameroid constrictors placed on a femoral artery in a mouse (stage one, day 1) and ligation of the femoral artery before excision (stage two, day 14).

distance to a significantly greater degree than resistance training programmes (mean difference 16 m, 95% CI 5–27 m)[137]. This finding could reflect that patients training on a treadmill would be expected to be able to walk further during a treadmill outcome assessment than those doing resistance training owing to a learning effect.

The current evidence on how exercise therapy might improve walking distance in patients with PAD has been described in a review published in 2021 (REF.[134]). Studies of lower extremity muscle biopsy samples from patients with PAD have shown muscle fibre denervation and reinnervation and an increase in markers of glycolysis after exercise therapy[134]. However, muscle capillary density does not seem to be significantly increased after exercise training[134,138]. A study that involved 35 patients with PAD and 41 control individuals undergoing supervised treadmill training showed that at study entry, patients with PAD had a fall in plasma nitrite concentrations in response to treadmill exercise, which was not seen in healthy controls[139]. After 3 months of supervised training, this exercise-induced fall in plasma nitrite concentration in patients with PAD was lost[139]. When considered alongside evidence that ingestion of inorganic nitrate increases walking distance in patients with intermittent claudication, this finding suggests that recovery of local NO production could contribute to the benefit of exercise therapy[140,141].

The uptake of supervised exercise training among patients with PAD has been reported to be low[142]. Supervised sessions are typically run in a central facility, which can require patients to travel long distances. Structured home-exercise programmes have been developed for patients with PAD and have been reported in meta-analyses of randomized controlled trials to improve walking distance[129,143,144]. The benefits of the programmes varied. McDermott and colleagues[145] conducted a trial of 194 patients with PAD who were randomly assigned to either a home-based, group-mediated cognitive behavioural walking intervention consisting of weekly, 90-min face-to-face group sessions or an attention control group. At 6 months, a mean improvement in 6MWT distance of 54 m (95% CI 33–74 m) was reported for the intervention group[145]. By contrast, a trial by the same investigators, in which 200 patients were randomly assigned to either a home programme consisting of a wearable activity monitor and four face-to-face weekly coaching sessions (progressing to monthly telephone coaching) or an attention control group, reported no benefit for the intervention[146]. The latter programme[146] involved less-intense coaching than the former one[145], and might have been less effective at promoting exercise training. Another trial showed that a home programme of high-intensity (stimulating moderate-to-severe ischaemia leg pain), but not low-intensity (stimulating no ischaemic leg pain), exercise overseen by weekly telephone coaching significantly improved walking distance[147]. Together, these findings suggest that exercise programmes need to involve frequent coaching to promote the high-intensity exercise needed to improve walking distance.

The AHA Council on Peripheral Vascular Disease has developed guidelines for optimal exercise programmes for patients with symptomatic PAD[106,136]. Although

the guidelines acknowledge that exercise programmes should be individualized to each patient, they provide specific advice on the recommended format. Treadmill or other walking-based exercise programmes, involving 30–50 min sessions three times per week for at least 12 weeks, are recommended. The intensity at commencement should be 40–60% of maximum baseline workload to induce moderate-to-severe leg pain during constant walking periods of 5–10 min. Every 1–2 weeks, the duration of the exercise session should incrementally increase. Lifelong maintenance of at least two exercise sessions per week is recommended[106,136].

Revascularization in patients without CLTI. Clinical guidelines suggest that revascularization is a reasonable treatment option for patients with intermittent claudication caused by aortoiliac or femoropopliteal occlusive disease who have an inadequate response to medical treatment and exercise[11–13]. A network meta-analysis of 46 clinical trials (n = 4,256) published since 2000 compared the effect of cilostazol, supervised exercise, home exercise and endovascular revascularization[129]. In the first year, home exercise, supervised exercise and a combination of supervised exercise and endovascular revascularization all significantly improved walking distance, but endovascular revascularization alone or cilostazol alone did not[129]. At 1–2 years, supervised exercise and a combination of supervised exercise and endovascular revascularization significantly improved walking distance, but home exercise did not (no data on cilostazol). At both short-term and mid-term follow-up, the combination of supervised exercise and endovascular revascularization provided the greatest improvement in walking distance, followed by supervised exercise alone[129]. None of the treatments was found to significantly improve walking distance beyond two years[129]. The analysis was limited by the small size of the available trials and the short follow-up period. The findings were broadly similar to findings from three earlier meta-analyses in suggesting that the combination of supervised exercise and endovascular revascularization achieves the greatest improvement in walking distance[135,148,149]. The lack of evidence for long-term improvement in walking distance for any of the available treatments is concerning. In many of the included trials, reporting on the requirement for subsequent revascularization or amputation, mortality or other adverse events was limited, making analysis of these important outcomes problematic[129]. In a meta-analysis of three trials involving a total of 457 patients who were randomly assigned to supervised exercise or supervised exercise plus endovascular revascularization, Pandey and colleagues[149] reported that the combination treatment reduced the risk of subsequent revascularization or amputation (OR 0.19, 95% CI 0.09–0.40). Despite this seemingly reassuring result, some concern about the safety of endovascular revascularization remains for several reasons. First, follow-up in the meta-analysis by Pandey and colleagues was only 12 months in two trials and 24 months in one trial. Second, long-term observational studies have shown that revascularization in patients with intermittent claudication is

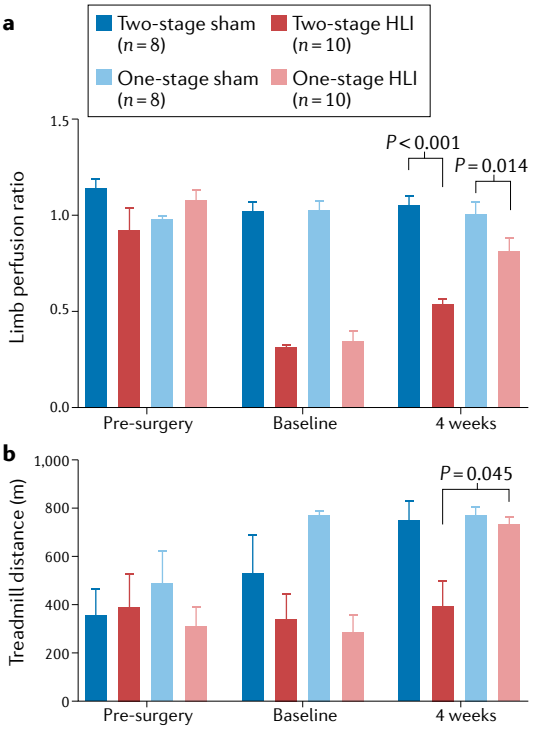

Fig. 6 | **Comparison of the hindlimb blood supply and function in the one-stage and two-stage HLI models of PAD. a** | The relative mean (standard error) hindlimb blood supply in mice undergoing the one-stage or two-stage hindlimb ischaemia (HLI) procedures or sham control procedures. At 4 weeks, hindlimb blood supply was still significantly reduced in the two-stage, but not the one-stage model, compared with sham controls. Statistical comparisons were performed using two-way ANOVA. **b** | The mean (standard error) ambulatory distance on a treadmill of mice undergoing the two types of HLI procedure. At 4 weeks, the ambulatory distance was significantly shorter in the two-stage model than in the one-stage model. Statistical comparisons were performed using two-way ANOVA. The graphs were generated using data from REF.[108]. PAD, peripheral artery disease.

associated with an increased risk of subsequent revascularization (HR 1.44, 95% CI 1.37– 1.51)[150], amputation (HR 4.52, 95% CI 2.15–9.54; HR, 4.22, 95% CI 1.09–16.31)[54,132] or death (HR 1.38, 95% CI 1.29–1.48)[150] compared with conservative management[54,132,150]. Third, a meta-analysis of 28 randomized trials (n = 4,663; 89% of patients with intermittent claudication) showed that treatment with paclitaxel-coated endovascular devices led to an increased risk of death (RR 1.68, 95% CI 1.15–2.47), causing widespread concern[151,152]. The FDA subsequently recommended that clinicians should inform patients of a potential increased risk of death with paclitaxel-coated devices[152]. Reassuringly, in a meta-analysis from 2021, no excess risk of death with paclitaxel-coated devices was reported[153]. However, more evidence is needed to advise patients without CLTI about the value and risk of revascularization. Given the large number of endovascular revascularization procedures performed worldwide, their high cost and reasonable concerns about safety, large randomized trials with long-term follow-up are needed to compare

the outcomes of endovascular revascularization with medical and exercise management alone for patients without CLTI[6,64]. The AHA has identified this issue as a key area for future research[6]. Given the safety concerns of revascularization, greater efforts to provide exercise therapy to patients with PAD but no CLTI are needed.

Revascularization for patients with CLTI. Revascularization is the established first-line treatment for CLTI, although this procedure is not always feasible[15]. The authors of the 2019 Global Vascular Guidelines examined the evidence and provided detailed recommendations for the management of patients with CLTI[15]. The techniques and evidence for both endovascular and open surgical revascularization in patients with CLTI were also discussed in a review published in 2018 (REF.[154]). Only one published large, randomized clinical trial has compared outcomes for endovascular and open surgical revascularization first approaches to managing patients with CLTI, with no difference in amputation-free survival reported (HR 0.89, 95% CI 0.68–1.17)[155]. However, endovascular revascularization techniques have substantially evolved since this trial was conducted, and the most appropriate management strategies for patients with CLTI are being investigated in several ongoing randomized trials[15,154]: for example, the BASIL-2 (bypass versus angioplasty)[156], BASIL-3 (angioplasty versus stenting)[157] and BEST-CLI (best endovascular versus best surgical therapy)[158] trials. In real-world clinical practice, the choice of revascularization technique for patients with CLTI is currently based on the vascular disease, presence of comorbidities and the experience and facilities available locally. Readers are referred to past reviews and the available guidelines for further information[15,154].

Prevention of MACE

Lipid-modifying drugs. The UK Heart Protection study[19] showed that therapy with 40 mg simvastatin reduced the incidence of MACE compared with placebo in patients with PAD (RR 0.78, 95% CI 0.71–0.85). Confirming the benefit of treatments that reduce plasma LDL-cholesterol levels, the FOURIER placebo-controlled,

Table 6 | **Novel therapies effective in animal models of peripheral artery disease**

HLI model	Species	Therapy	Effect on limb blood flow[a]	Other findings	Targets	Ref.
One stage	Sprague–Dawley rats	NO donor (MPC-1011)	Increased by day 6	Increased capillary density, arteriole diameter and angiogenesis, associated with upregulation of angiogenesis-promoting cytokines	Improved arteriogenesis and angiogenesis	111
One stage	BALB/c mice	BM-MSCs induced to differentiate into endothelial cells in vitro	Increased by day 28	Increased cell engraftment and capillary density	Improved engraftment of angiogenesis precursor cells	112
One stage	C57BL/6 mice	*N*-acetyl cysteine	Increased by day 7	Increased treadmill exercise capacity, capillary density and circulating EPC levels and reduced circulating markers of ischaemia-induced ROS	The reduction in the levels of ischaemia-induced ROS had anti-angiogenesis effects	113
One stage	C57BL/6 mice	IL-10	Increased by day 3	Changed macrophage phenotype to promote angiogenesis	Modulation of inflammation to promote angiogenesis	114
One stage	*Ldlr*$^{-/-}$ Leiden mice	Anti-galectin 2 antibodies	Increased by day 14	Increased arteriolar diameter and number of perivascular M2 macrophages	Modulation of inflammation to promote arteriogenesis	115
One stage	Immuno-compromised mice	ECFCs overexpressing *Nox4*	Increased by day 7	Increased expression of genes encoding pro-angiogenesis and pro-arteriogenesis proteins, including eNOS, DPP4, endoglin, HBEGF, MMP9, osteopontin and SDF1	Improved arteriogenesis and angiogenesis	116
One stage	BALB/c mice	AAV-*Pfkfb3* vector	Increased by day 7	Reduced limb necrosis and improved muscle histology	Upregulation of glycolysis in muscle and endothelial cells	117
One stage	Apolipoprotein E-deficient mice	MALP2	Increased by day 3	Increased collateral artery diameter, pericollateral macrophage accumulation and gastrocnemius capillary density	Improved arteriogenesis and angiogenesis	119
Temporary tourniquet	C57BL/6 mice	Mitochondrial transplantation	Not assessed	Reduced leg muscle infarction and improved leg function	Corrected ischaemia–reperfusion injury of muscle mitochondria	118

Preference was given to studies published in 2021 or 2020. [a]Assessed by laser Doppler. AAV, adeno-associated virus; BM-MSCs, bone-marrow-derived mesenchymal stem cells; DPP4, dipeptidyl peptidase 4; ECFC, cord-blood-derived endothelial colony-forming cell; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; HBEGF, proheparin-binding EGF-like growth factor; HLI, hindlimb ischaemia; MALP2, macrophage-activating lipopeptide 2; MMP9, matrix metalloproteinase 9; NO, nitric oxide; ROS, reactive oxygen species, SDF1, stromal cell-derived factor 1.

randomized trial[8] showed that therapy with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab significantly reduced the risk of MACE in patients with PAD (HR 0.73, 95% CI 0.59–0.91). Notably, participants needed to have been treated or failed treatment with a statin to be eligible for enrolment. Evolocumab also reduced the risk of major adverse limb events (HR 0.58, 95% CI 0.38–0.88), suggesting that reducing plasma LDL-cholesterol levels limits the progression of lower limb atherothrombosis[8]. The ODYSSEY OUTCOMES trial[159] showed that, among 18,924 patients with acute coronary syndrome, therapy with the PCSK9 inhibitor alirocumab reduced the combined risk of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospital admission (HR 0.85, 95% CI 0.78–0.93). In participants with polyvascular disease (coronary and cerebrovascular disease plus PAD), alirocumab did not significantly reduce the absolute rate of the primary outcome (13.0% reduction (95% CI −2.0% to 28.0%)) but significantly reduced the absolute rate of all-cause death by 16.2% (95% CI 5.5%–26.8%)[160]. Treatment with eicosapentaenoic acid to reduce plasma triglyceride levels has also been reported to reduce the risk of MACE in two randomized trials[161,162].

Antihypertensive drugs. The HOPE study[163] is the only randomized trial of an antihypertensive drug in which outcomes are reported for patients with PAD. Therapy with ramipril (2.5 mg) reduced the risk of MACE (HR 0.75, 95% CI 0.61–0.92) in this population[163]. The SPRINT trial[164] investigators reported that a strategy of lowering systolic blood pressure to <120 mmHg reduced major vascular events (HR 0.75, 95% CI 0.64–0.89) and mortality (HR 0.73, 95% CI 0.60–0.90) compared with a target of <140 mmHg. Although the SPRINT trial included patients with PAD, outcomes for this subgroup were not reported separately[164]. Another randomized trial of intensive blood-pressure-lowering therapy in patients with diabetes reported no benefit[165]. The threshold to which blood pressure should be lowered in patients with PAD remains unclear.

Antidiabetic drugs. The ACCORD trial[166] investigators reported that, among patients with diabetes, intensive blood-glucose control reduced the risk of lower extremity amputations compared with standard glucose control (HR 0.69, 95% CI 0.48–0.99). Therapy with the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin was shown to reduce the risks of cardiovascular death (HR 0.57, 95% CI 0.37–0.88) and all-cause death (HR 0.62, 95% CI 0.44–0.88) in a randomized trial in patients with PAD and diabetes[167]. Two trials involving 10,142 patients with diabetes and high cardiovascular risk showed that the SGLT2 inhibitor canagliflozin reduced the risk of MACE (HR 0.86, 95% CI 0.75–0.97) but increased the risk of amputation (HR 1.97, 95% CI 1.41–2.75)[168]. On the basis of a review of the evidence, in 2017 the FDA added a boxed warning that the risk of amputation was very high in relation to the potential benefit of canagliflozin. However, in 2020, this warning was removed on the basis of new data from three clinical trials.

The VERTIS CV trial[169] investigators randomly assigned 8,246 patients with type 2 diabetes and cardiovascular disease (19% with PAD) to receive the SGLT2 inhibitor ertugliflozin or placebo. The risk of MACE was similar in both groups (HR 0.97, 95% CI 0.85–1.11)[169]. A secondary analysis from the DECLARE-TIMI 58 trial[170], which involved 17,160 patients with type 2 diabetes (6% with PAD), showed that the effect of the SGLT2 inhibitor dapagliflozin did not vary significantly between participants with or without PAD. The main findings of the trial were that dapagliflozin did not reduce the risk of MACE (HR 0.93, 95% CI 0.84–1.03) but did reduce the risk of cardiovascular death or hospital admission for heart failure (HR 0.83, 95% CI 0.73–0.95)[171]. Among patients with PAD, no significant difference in the risk of limb ischaemic events (HR 0.93, 95% CI 0.71–1.23) or amputation (HR 1.51, 95% CI 0.94–2.42) was observed between the dapagliflozin and placebo groups[170].

Antithrombotic drugs. A post hoc exploratory analysis of the CAPRIE trial[172] showed that therapy with 75 mg clopidogrel reduced the risk of MACE (RR 0.76, 95% CI 0.64–0.91) compared with 100 mg aspirin. In the EUCLID trial[49], 13,885 patients with symptomatic PAD were randomly assigned to ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). No difference in the rate of MACE was reported (HR 1.02, 95% CI 0.92–1.13)[49]. The COMPASS trial[9] investigators tested low-dose rivaroxaban (2.5 mg twice daily) in addition to 100 mg aspirin compared with aspirin alone in 7,470 patients with peripheral vascular disease (4,129 with symptomatic PAD). Low-dose rivaroxaban plus aspirin reduced the risk of MACE (HR 0.72, 95% CI 0.57–0.90), major adverse limb events (HR 0.54, 95% CI 0.35–0.84) and major amputation (HR 0.30, 95% CI 0.11–0.80) compared with aspirin alone[9]. However, the dual therapy was associated with an increased risk of major bleeding (HR 1.61, 95% CI 1.12–2.31) but not fatal or critical organ bleeding (HR 1.10, 95% CI 0.59–2.05)[9]. In the VOYAGER PAD trial[173], low-dose rivaroxaban (2.5 mg twice daily) in addition to 100 mg aspirin was compared with aspirin alone in patients with symptomatic PAD undergoing lower extremity revascularization. The combined therapy reduced the risk of a composite of major adverse limb and cardiovascular events (acute limb ischaemia, major amputation due to ischaemia, myocardial infarction, ischaemic stroke or cardiovascular death; HR 0.85, 95% CI 0.76–0.96)[173]. The findings of the COMPASS[9] and VOYAGER PAD[173] trials provide strong support for the use of dual therapy with low-dose rivaroxaban plus aspirin in patients with PAD, after consideration of the risk of bleeding of the patient and local accessibility to the therapy.

Smoking cessation. Approximately one-third of patients with PAD are current smokers[1,48]. Therefore, effective interventions to aid smoking cessation are crucial in reducing the risk of major adverse events[1,48]. Few randomized controlled trials of these interventions have been performed in patients with PAD[7]. Only one trial

has shown a benefit for a smoking-cessation intervention (a minimum of six sessions of cognitive behavioural counselling and advice about medication to treat nicotine withdrawal) in 124 patients with PAD who smoked[174]. Patients receiving the smoking-cessation intervention were more likely to use varenicline (a drug used to aid in smoking cessation) during the study than control participants[174]. The number of patients with biochemically verified smoking abstinence at 6 months was 21.3% in the intervention group and 6.8% in the control group ($P = 0.023$)[174]. Whether these effects are durable and can be generalized is unclear.

Improving implementation of treatments

Guideline-recommended therapies that reduce major adverse events are not effectively implemented in patients with PAD[1,175]. In a study of 783 patients with PAD, only one-third had plasma LDL-cholesterol levels at therapy targets of <1.8 mmol/l (REF.[1]). Similarly, in another study, 31% of patients with PAD had a systolic blood pressure greater than the treatment target of 140 mmHg (REF.[175]). Smoking cessation, diabetes control and prescription of antithrombotic drugs have also been reported to be suboptimal in these patients[1,175,176]. Ensuring effective implementation of medical therapies is an urgent issue in the management of patients with PAD and is likely to offer the most achievable means of preventing major adverse events.

A range of interventions have been proposed to improve implementation of evidence-based medical therapies[7]. These include case managers to improve communication between patients and specialists, and technology-enabled communication devices, such as medication reminders and online education programmes[7]. A cluster-randomized controlled trial of a quality improvement programme — including decision support tools, case managers, audit and feedback — showed significant improvement in the prescription of evidence-based medications in patients with various vascular diseases[177]. Another randomized trial demonstrated that an intervention consisting of a personalized website and education from a nurse practitioner significantly improved risk-factor control in patients with cardiovascular disease[178].

Quality improvement programmes that educate, audit and feed back to physicians and patients are likely to be needed for long-term success. In this regard, financial incentives to encourage prescription of evidence-based cardiovascular medications are being used in some countries. In the Millions Heart Cardiovascular Risk Reduction Model, providers are paid for measuring and reducing cardiovascular risk in Medicare patients[179]. The effect of this model is being examined in an ongoing large, randomized, controlled trial[179]. In a 2021 interim report from the trial, significant improvements in systolic blood pressure and plasma LDL-cholesterol levels were reported for the model comparison with standard care[179]. The trial will also examine the effect of the model on cardiovascular events. If proved effective, similar financial incentive models could be used globally to optimize uptake of evidence-based cardiovascular therapies.

Cell therapy
Administering stem or progenitor cells to encourage angiogenesis.

Treatments under investigation

Limb symptoms and tissue loss

Repurposed medications and supplements. Atherosclerosis has been reported to induce dysfunction in endothelial NO synthase (uncoupling) so that production of NO is impaired[180]. This effect might partly explain the microvascular dysfunction reported in patients with PAD[181], who have impaired endogenous capacity to produce NO. Exogenous sources of NO, such as inorganic nitrates, have therefore been proposed as a means of correcting microvascular dysfunction[182]. Several small, randomized, controlled trials have shown that inorganic nitrate, delivered as concentrated beetroot juice, increased walking distance in patients with intermittent claudication[140,141]. Oxygen-derived free radicals interfere with NO generation in patients with PAD[183]. The findings from a few small trials have indicated that antioxidants, such as derivates of dark chocolate and a mitochondria-targeted antioxidant (MitoQ), improve walking distance in patients with PAD[184–186]. The angiotensin-receptor blocker telmisartan has also been reported to significantly improve walking distance in a randomized, placebo-controlled trial in 36 patients with PAD and no CLTI[187]. Two small, randomized trials performed in the 1980s and 1990s showed that the antidiabetic drug metformin improved leg blood supply and walking distance in patients with PAD[188,189]. Finally, a randomized, placebo-controlled trial of 66 patients with PAD showed that 125 mg, but not 500 mg, of the polyphenol resveratrol significantly improved walking distance in the setting of PAD, based on a pre-set P value of <0.1 (REF.[190]). Larger and longer-term studies are needed to determine whether any of these findings can be replicated and these therapies applied safely in patients with PAD.

Cell therapies. A systematic review published in 2019 identified 27 randomized controlled trials ($n = 1{,}186$) that tested various autologous stem cells[191]. All the studies were small ($n = 10$–160) and many provided only limited evidence of PAD diagnosis[191]. Some of the study participants are likely to have had neuropathic rather than ischaemic ulcers. The cell therapies studied included bone-marrow-derived mononuclear cells, peripheral blood mononuclear cells, bone-marrow aspirates, bone-marrow-derived mesenchymal cells and peripheral-blood-derived angiogenic cell precursors[191]. None of the trials was considered to be at low risk of bias, based on failure to report completion of all elements of the Cochrane risk of bias assessment[191]. Overall, autologous stem cell therapy was reported to significantly improve the likelihood of foot ulcer healing (OR 4.31, 95% 2.94–6.30) and reduce the risk of any lower limb amputation (OR 0.50, 95% 0.36–0.69), but not major amputation (OR 0.66, 95% 0.42–1.03). Autologous stem cell therapy reduced the rest pain score (mean difference 1.61, 95% CI 1.21–2.01) and improved pain-free walking distance (mean difference 178, 95% CI 128–228)[191]. Autologous stem cell therapy was also reported to significantly increase ABI (mean difference 0.13, 95% CI 0.10–0.17) and increase foot transcutaneous oxygen pressures (mean difference 12.6, 95% CI 5.7–19.5)[191].

Gene therapy
Administering harmless viruses that have been modified to carry a gene of interest into the local tissue.

The safety of the cell therapy was not uniformly or well reported.

Although these findings suggest that autologous stem cell therapy could be a promising therapy, several challenges remain. Harvesting bone marrow or other autologous cells is invasive and expensive. The type of cell population that is most effective is unclear. Isolating sufficient cell numbers of particular populations can be difficult and requires in vitro culture or modification, which is not easily standardized and is expensive. A possible solution is to use colony-stimulating factors to mobilize the patient's stem or progenitor cells, with the aim that these cells will engraft at sites of peripheral artery occlusion to promote angiogenesis and arteriogenesis. The effect of administration of granulocyte–macrophage colony-stimulating factor (GM-CSF) via subcutaneous injection six times over 2 weeks was examined in 210 patients with PAD in a randomized, placebo-controlled trial[192,193]. In the primary analysis, GM-CSF therapy did not significantly improve 6MWT or treadmill walking distance at 12 or 26 weeks[192]. An exploratory analysis found that GM-CSF significantly improved 6MWT distance in white ($n = 64$) but not in Black ($n = 141$) participants[193]. No clear explanation for this racial disparity in effect was found. Overall, these findings suggest potential therapeutic benefits of cell therapy in PAD. Further research is needed to optimize the mode of treatment and test it in large, well-designed trials for specific PAD indications, such as unresolved CLTI.

Growth factor and gene therapies. Several proteins and DNA and RNA products have been developed with the aim of being administered to the limb of patients with PAD to promote revascularization through stimulating angiogenesis[194–197]. Overall, trials of these therapies have reported disappointing results. One Cochrane systematic review showed that growth factors had no effect on major amputation (OR 0.99, 95% CI 0.71–1.38) and that the included trials had a high risk of bias and imprecision[196]. Another Cochrane systematic review highlighted that the evidence for an improved likelihood of foot ulcer healing with gene therapy was of low quality (OR 2.16, 95% CI 1.02–4.59)[197]. A phase II trial involving 200 participants with CLTI showed that administration of a plasmid engineered to express two isoforms of hepatocyte growth factor significantly reduced the severity of foot pain (coprimary outcome) and increased the likelihood of complete ulcer healing (secondary outcome) but had no significant effect on mean ulcer size (coprimary outcome)[194]. No significant improvement in amputation rate or markers of foot blood supply was found[194]; therefore, how the demonstrated benefit was achieved is unclear. Overall the place of gene and growth factor therapies in treating PAD remains uncertain, despite clinical trials being conducted in this area for more than a decade.

Prevention of MACE

The rate of MACE is now widely recognized to be higher among patients with PAD than in those with most other cardiovascular diseases. Industry-run clinical trials are focusing on PAD[2,8,9], and novel therapies being developed are likely to be tested in these patients. Drugs being designed by pharmaceutical companies to target untreated risk factors, such as increased plasma lipoprotein(a) levels, inflammation and prothrombotic tendency, include interfering RNAs against *PCSK9* and *LPA*, interleukin-blocking antibodies and repurposed rheumatoid disease drugs[198–201].

Conclusions

PAD is present in 6% of adults and is associated with substantially impaired function, reduced QOL and high risk of major adverse events. Limited pathology studies have suggested the importance of thrombosis in PAD pathogenesis. Medications effective at modifying key risk factors for PAD have been shown to substantially reduce the risk of adverse events. However, these drug therapies are not optimally implemented in clinical practice and a crucial requirement for future research is to clarify the reasons and develop solutions for poor implementation. The therapies currently available for the functional impairment caused by PAD have several limitations, including poor efficacy and durability. Research is needed to develop better treatments for PAD-related walking impairment. Most importantly, medical therapies are needed for CLTI as an adjunct to revascularization and for when revascularization is unsuccessful or not possible. Exciting work on genetic variants and other new risk factors is ongoing and promises to identify novel treatment targets for PAD.

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Competing interests

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